REMARKS

Claims 1-3, 5-6, 9-12, 19-36, and 44 are pending in this application. Claims 19-36 were withdrawn from consideration. Claims 1-3, 5-6, 9-12, and 44 are currently under examination; all claims have been rejected under 35 U.S.C. § 112, first paragraph.

By this amendment, claim 1 has been amended without prejudice or disclaimer of any previously claimed subject matter. Support for the amendment to claim 1 is found, *inter alia*, in claim 1 as originally filed, and at page 10, lines 9-13.

The amendments are made solely to clarify the nature of the nature of the invention and to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants expressly reserve the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicants have carefully considered the points raised in the Office Action and discussed in the interview, and believe that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance.

Rejections under 35 U.S.C. §112, first paragraph

Claims 1-3, 5-6, 9-12, and 44 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants respectfully submit that the amended claims are enabled, and would like to bring the following facts and legal arguments to the Examiner's attention.

SECTION I: FACTS TO BE CONSIDERED

Applicants would like to emphasize the following facts that Michael Cornfeldt has laid out in the attached declaration.

1) The instant application claims a method of treating negative symptoms or the cognitive defects associated with schizophrenia. Specifically, cells producing dopamine or a dopamine precursor, such as retinal pigmented epithelial (RPE) cells, are implanted into the prefrontal cortex of the brain, in order to provide dopamine to this region. As discussed below, dopamine deficiency in the prefrontal cortex is an underlying cause of the negative symptoms and/or cognitive deficits seen in schizophrenia.

2) Schizophrenia is characterized by two main types of symptoms. "Positive" symptoms include delusions or hallucinations, while the negative/cognitive deficit symptom complex includes affective flattening, alogia, avolition, anhedonia (loss of interest or pleasure), social withdrawal and apathy.

3) Positive and negative symptoms are thought to have opposite causes.

    - Although positive symptoms are caused by *excess* dopamine function in the mesolimbic area of the brain, negative symptoms are thought to be caused by *decreased* dopamine tone in another area of the brain, i.e., the prefrontal cortex. *See, e.g.*, Davis *et al.*, Am. J. Psychiatry 148:1474-1486 (1991) (of record), at abstract; at page 1479, second column; at page 1481, second column. For example, Brozoski *et al.* demonstrated in a rhesus monkey model that when the prefrontal cortex was selectively depleted of dopamine by local injection of the neurotoxin 6-OHDA, cognitive function declined. Brozoski *et al.*, Science, 205:1929-931 (1979) (of record).

4) Positive symptoms are treated by dopamine antagonists. Administration of dopamine (or its precursors) has a therapeutic effect on negative symptoms and cognitive deficits in schizophrenics. Inanaga *et al.*, Folia Psychiatr Neurol Jpn (1975), 29:123-43 (of record).

5) In addition, administration of dopamine or its precursors reverses cognitive defects caused by loss of dopamine in the *prefrontal cortex* specifically.

    - For instance, Brozoski *et al.* showed that the dopamine precursor L-DOPA reversed cognitive impairment caused by neurotoxin-induced dopamine

depletion in the prefrontal cortex of monkeys. Brozoski *et al.*, at page 931, second column.

- Similarly, Fernandez-Ruiz *et al.* showed that the dopamine precursor L-DOPA significantly improved prefrontal cortex-related activities such as memory and spatial delayed response tasks. Fernandez-Ruiz *et al.*, Psychopharmacology, 147: 104-107 (1999). Fernandez-Ruiz *et al.* treated rhesus monkeys with a dopaminergic neurotoxin MPTP in order to mimic cognitive defects often seen in Parkinson's Disease. The last-received Office Action of December 15, 2004, stated that in Fernandez-Ruiz the MPTP lesions were in the striatum of the brain instead of the prefrontal cortex. Applicants respectfully disagree. Fernandez-Ruiz *et al.* noted that MPTP causes disruption of the "prefronto-striatal system," which includes the prefrontal cortex as well as the striatum. Fernandez-Ruiz *et al.*, at page 104, second column. Fernandez-Ruiz *et al.* also noted that the prefrontal cortex in addition to the striatum is impaired in both Parkinson's disease patients and MPTP-treated monkeys. *Id.* Fernandez-Ruiz *et al.* administered L-DOPA systemically to the test monkeys through oral administration so that L-DOPA reached the prefrontal cortex as well as the striatum. Fernandez-Ruiz *et al.*, at page 105, first column. Fernandez-Ruiz *et al.* concluded that "L-DOPA reverses the MPTP-induced impairment by acting on *both* components of the fronto-striatal system" - that is, both the prefrontal cortex and the striatum. Fernandez-Ruiz *et al.*, at page 107, first column (emphasis added). Fernandez-Ruiz *et al.* therefore demonstrate that administration of the dopamine precursor L-DOPA has a therapeutic effect on cognitive defects caused by disruption of the fronto-striatal system, including the prefrontal cortex.

6) The Office Action contends that "studies that teach administration of L-DOPA do not provide specific guidance with regard to the claimed invention which is quite distinct, involving administration of cells that produce dopamine or a dopamine precursor." Office Action at page 4, first paragraph. Applicants respectfully disagree. Actually, the preferred cells of the invention (RPE cells) themselves produce L-DOPA. Watts *et al.*, J Neur. Tr. Suppl. 65:215 (2003), at page 217. In any case, Applicants would like to address this argument by bringing the following facts to the Examiner's attention.

- First, cell-based dopamine replenishment had been effectively used before April 1999 in treating animal models of dopamine deficiency disorders, such as Parkinson's disease. For instance, Subramanian *et al.* found that the implantation of dopamine-producing RPE cells of the invention into the brain of monkey models of Parkinson's disease reversed parkinsonian symptoms, just as administration of L-DOPA itself would. The animals were treated with 10,000

RPE cells/site at 5 sites (*i.e.*, 5 x 10^5 cells in total). *See* Subramanian et al. (1998) Abs. Amer. Soc. for Neural Transpl., 2-5; Subramanian et al. (1998) Abs. 5th International Cong. Parkinson's Disease and Movement Disorders, New York; Subramanian et al. (1999) Parkinsonism and Related Disorders, 5, S111.

- As discussed by Mr. Cornfeldt, a post-filing publication by Watts et al. co-authored by Mr. Cornfeldt discloses that transplantation of dopamine-producing RPE cells into the brain resulted in long term amelioration of Parkinson's disease symptoms. Watts et al., Neurology 56, Suppl. 3, Abstract P04.102 (Apr 2001) (of record). Specifically, Watts et al. demonstrated that the implantation of 325,000 dopamine-producing RPE cells into the brain of parkinsonian patients produced "long term amelioration of motor and behavioural deficits." *Id.* Watts et al. also reported that the therapeutic effects of RPE cell transplantation had lasted for 24 months as of 2003. In fact, the therapeutic effects are still evident in these patients today, more than four years later. Watts et al. found that the transplantation of RPE cell was as therapeutically effective as the administration of L-DOPA itself. *Compare* Watts et al. (2003) (transplantation of 325,000 RPE cells into the brain of parkinsonian patients improved UPDRS-Motor scores by approx. 30-50%) with Rascol et al., Mov Disord. 13(1):39-45 (1998) (disclosing that oral doses of L-DOPA improved UPDRS-Motor scores of parkinsonian patients by 44%).

7) Watts et al. used the cell implantation methods and parameters taught in the instant application and provides post-filing evidence that these teachings of the application are correct. The number of cells used by Watts et al. on humans (i.e., 3 x 10^5 cells) falls within the guidelines of the instant application (which states that 10^3-10^7 cells, preferably 10^5-10^6 cells, should be used). Watts et al. attached the preferred cells of the invention (RPE cells) to the preferred microcarrier of the invention (gelatin microbeads of 100 μm diameter), and implanted these cells into Parkinson's disease patients using the methods taught in the invention (MRI-guided stereotaxic surgery).

8) Although the Office Action acknowledges that the art at the time of filing teaches cell-based dopamine replacement therapy for *Parkinson's disease*, the Office Action contends that this teaching does not provide guidance for treatment of *schizophrenia*, which has its own distinct etiology. However, as Mr. Cornfeldt explains in the attached declaration, **doses of dopamine (or dopamine precursors) that are effective to treat Parkinson's disease should be more than sufficient to treat the cognitive defects and negative**

symptoms of schizophrenia. For instance, the oral dosage of L-DOPA used for Parkinson's disease is the same as or higher than the effective dosage required for schizophrenia. *Compare* Physician's Desk Reference (oral doses of 1-8 gm of L-DOPA for Parkinson's disease) with Inanaga *et al.*, Folia Psychiatr Neurol Jpn (1975), 29:123-43 (oral doses of 400-1200 mgs of L-DOPA are effective to treat negative symptoms and/or cognitive deficits of schizophrenia). **Thus, any number of cells shown to provide sufficient dopamine to produce a therapeutic effect in Parkinson's disease should be sufficient to treat schizophrenia**. The application's guidelines regarding the number of cells to use cover the number of cells shown by Watts *et al.* to be effective in ameliorating motor and behavioral defects associated with Parkinson's disease. Thus the application does provide guidance that is sufficient for the treatment of the negative symptoms and/or cognitive defects of schizophrenia.

SECTION II: LEGAL DISCUSSION

35 U.S.C. 112, first paragraph requires that the specification, when filed, contains sufficient information regarding the subject matter of the claims to enable one skilled in the pertinent art to make and use the claimed invention without undue experimentation. MPEP § 2164.01; *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916). In order to make a rejection, the Examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993); MPEP § 2164.04. The examiner should specifically identify what information is missing and why one skilled in the art could not supply the information without undue experimentation. See MPEP § 2164.06(a). Determining enablement is a question of law based on underlying factual findings. MPEP § 2164.01. Any conclusion of non-enablement must be based on evidence as a whole. MPEP § 2164.01(a); *In re Wands*, 858 F.2d 731, 738 (Fed. Cir. 1988). The Examiner must provide specific technical reasons for any enablement rejection; and should never make the determination based on personal opinion. MPEP § 2164.05.

The last-received Office Action of December 15, 2004, for this application rejected all pending claims as non-enabled, stating that the specification and the art at the time of filing do not provide specific guidance with regard to the claimed invention, which involves administration of cells that produce dopamine or a dopamine precursor. Specifically, the Office Action stated that the cells "must produce dopamine or a dopamine precursor at the appropriate location, in an amount sufficient to alleviate a symptom of schizophrenia," and that the "references cited do not provide evidence of an enabling disclosure for such a protocol." Office Action of December 15, 2004, at 4. The Office Action also reasoned that the art at filing only disclosed administration of dopamine-producing cells in animal models, so that therapy for humans was not enabled. The Office Action finally noted that studies involving the administration of L-DOPA do not provide specific guidance on the administration of dopamine-producing *cells*. *Id.*

Applicants respectfully disagree. The instant application teaches types of cells and types of support matrices appropriate for use in the claimed method. See, for example, page 12, line 25 to page 21, line 13. The application teaches how to make the claimed cell support complex. See, for example, page 21, line 15, to page 22, line 6. The application teaches how to administer of the claimed cell/support complex to the prefrontal cortex of a patient with schizophrenia. See, for example, page 22, line 11 to page 23, line 21. The application provides guidelines as to site and means of administration of the complex using sterotaxic surgery, and notes that methods of delivering cells to a particular site in the brain would be known to those of skill in the art. See, for example, page 22, line 8 to page 23, line 11. The application also describes examples of negative symptoms of schizophrenia and standard methodology by which the symptoms may be assessed so that alleviation of a negative symptom can be determined. See, for example, page 7, line 21, to page 8, line 4, and page 23, lines 22-31. Finally, the instant application teaches the number of cells that must be administered to produce therapeutic levels of dopamine. See, e.g., page 23, lines 7-10 (10^3-10^7 cells, preferably 10^5 to 10^6 cells, *e.g.*, RPE cells, should be used).

Michael Cornfeldt has provided in his declaration sound reasons why the Examiner's conclusion is not warranted. Mr. Cornfeldt is a co-author of a post-filing publication by Watts *et al.*, which discloses that dopamine-producing RPE cells implanted into the brain of human patients resulted in long term amelioration of Parkinson's disease symptoms. Watts *et al.*, Neurology 56,

Suppl. 3, Abstract P04.102 (Apr 2001) (of record). As Mr. Cornfeldt notes, Watts *et al.* used the cell implantation methods and parameters taught in the instant application and provide post-filing evidence that these teachings of the application are correct. Specifically, Watts *et al.* demonstrated that the implantation of 325,000 dopamine-producing RPE cells into the brain of parkinsonian patients produced "long term amelioration of motor and behavioural deficits." Watts *et al.* (2001). Watts et al. also reported that the therapeutic effects of RPE cell transplantation had lasted for 24 months as of 2003. In fact, the therapeutic effects are still evident in these patients today, more than four years later. What is more, the data presented in Watts et al. shows that the transplantation of RPE cell was as therapeutically effective as the administration of L-DOPA itself. Compare Watts et al. (2003) (transplantation of 325,000 RPE cells into the brain of parkinsonian patients improved UPDRS-Motor scores by approx. 30-50%) with Rascol et al., Mov. Disord. 13(1):39-45 (1998) (disclosing that oral doses of L-DOPA improved UPDRS-Motor scores of parkinsonian patients by 44%).

The Office Action attempts to distance the claimed invention from the enabling teachings of the art at the time of filing by asserting that although the art at the time of filing discloses cellular dopamine replacement therapy for *Parkinson's disease*, it does not provide guidance for treatment of a patient with *schizophrenia*, which has its own distinct etiology. Office Action at 4. The Office Action concludes that the "instant specification does not teach how to generate dopamine levels that are sufficient to reduce a symptom of *schizophrenia.*" *Id.* (emphasis added).

Applicants respectfully disagree. As the Examiner has acknowledged, the art at the time of filing teaches cell-based dopamine replenishment therapy for cognitive and motor symptoms of Parkinson's disease. As Mr. Cornfeldt points out, these symptoms are associated with the prefronto-striatal system that includes the prefrontal cortex. (See attached Declaration, at paragraph 7). Mr. Cornfeldt also points out that **doses of dopamine (or dopamine precursors) that are effective to treat Parkinson's disease are more than sufficient to treat the cognitive defects and negative symptoms of schizophrenia.** (See attached Declaration, at paragraph 13). **For instance, the oral dosage of L-DOPA used for Parkinson's disease is the same as or higher than the**

effective dosage required for schizophrenia. *Compare* Physician's Desk Reference (oral doses of 1-8 gm of L-DOPA for Parkinson's disease) with Inanaga *et al.*, Folia Psychiatr Neurol Jpn (1975), 29:123-43 (oral doses of 400-1200 mgs of L-DOPA are effective to treat negative symptoms and/or cognitive deficits of schizophrenia). **Thus, as stated by Mr. Cornfeldt, any number of cells shown to provide sufficient dopamine to produce a therapeutic effect in Parkinson's disease should be sufficient to treat schizophrenia.** (See attached Declaration, at paragraph 13). The application's guidelines regarding the number of cells to use cover the number of cells shown by Watts *et al.* to be effective in ameliorating motor and behavioral defects associated with Parkinson's disease. (See attached Declaration, at paragraph 11). Thus the application does provide guidance that is sufficient for the treatment of the negative symptoms and/or cognitive defects of schizophrenia.

In the last Office Action of December 15, 2004, however, the Examiner persisted in the view that "development of cell therapy protocols has been an enormous challenge," and argues that "[c]onsiderable experimentation" would be required to actually provide an enabled protocol for achieving the desired treatment effect. Office Action, at 4. "In view of the state of the art and unpredictability in the art, for reasons of record, such experimentation is not considered routine, but rather would rise to the level of undue experimentation." *Id.* at 4-5.

Applicants respectfully disagree. As explained, the test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Even lengthy and complex experimentation is not necessarily undue, if the art typically engages in such experimentation. *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). Applicants respectfully submit that the burden is on the Examiner to establish a reasonable basis to question the enablement provided for the claimed invention; and in order to be reasonable, the rejection must be objectively based on evidence as a whole, rather than personal opinion. Mr. Cornfeldt's declaration provides a wealth of sound evidence to show that the guidelines of the specification are indeed enabling in the context of the state of the art at filing. Mr. Cornfeldt has identified various scientific publications demonstrating that dopamine-producing RPE cells of the

invention were as effective in ameliorating certain symptoms of Parkinson's disease as L-DOPA itself. The Examiner has produced no factual evidence that would refute these assertions. Thus, the Examiner's assertion that claimed methods are not enabled, especially in the face of such evidence to the contrary, is not enough to meet the Examiner's burden to provide a reasonable basis for a rejection on the grounds of nonenablement. Applicants respectfully request the Examiner to indicate if there is *any* reference or other evidence that would establish a reasonable basis for the conclusion that the claimed invention would require undue experimentation. Alternatively, Applicants would be grateful if the Examiner could supply an affidavit taking official notice that it would require undue experimentation to practice the claimed invention at the time of filing.

Lastly, the Examiner appears to suggest that cell-based therapy for Parkinson's disease is not enabling for a similar cell-based therapy for schizophrenia because the sites of administration are different. Office Action at 4. Applicants respectfully disagree. The specification teaches with great precision that the cell-support complex must be administered to the prefrontal cortex, to alleviate cognitive deficits associated with schizophrenia. *See, e.g.*, page 22, lines 13-16. As discussed above, the prefrontal cortex is implicated in both Parkinson's disease and schizophrenia. Lastly, the techniques of stereotactic surgery were well established, allowing implantation into any part of the brain with great control and precision as of April 9, 1999. (See attached Declaration, at paragraph 14).

Thus, the weight of the evidence clearly shows that in light of the teachings of the art at the time of filing, the instant specification would have enabled a skilled person to make and use the claimed invention without undue experimentation. The burden is on the Examiner to establish a reasonable basis for a conclusion of non-enablement. Applicants request Examiner to indicate if there is *any* reference or other evidence that supports the Examiner's assertion that in view of the state of the art and unpredictability in the art, undue experimentation would be needed to practice the claimed invention. Alternatively, Applicants would be grateful if the Examiner could supply an affidavit taking official notice that any required experimentation relating to the claimed invention would be undue.

In sum, Applicants submit that the pending claims fall within the subject matter that is described and enabled by the specification. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 112, first paragraph.

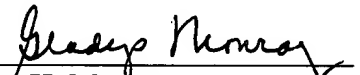
CONCLUSION

Applicants believe that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If the Examiner feels that a telephone interview would serve to facilitate resolution of any outstanding issues, the Examiner is encouraged to contact Applicants' representative at the telephone number below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, Applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 311772000600. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: February 13, 2006

Respectfully submitted,

By 

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